

## University of Groningen

### Endocarditis

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## Summary, discussion and conclusion



## Summary

Despite many efforts and developments in the last decades, mortality in patients with infective endocarditis did not change largely. Therefore, there is still room for improvement and optimization of care for patients with suspected endocarditis. In this thesis we have investigated several diagnostic and therapeutic links in the chain of care for these patients. We set up a multidisciplinary research group of representatives from various medical disciplines involved in caring for endocarditis patients, which we called IDENTICAL. The following section summarizes the most important messages from this thesis

### **New methods to diagnose infective endocarditis**

The first part of this thesis focussed on new methods to diagnose endocarditis.

In **Chapter 2** a systematic literature review was performed to critically appraise the evidence for the diagnostic performance of non-invasive imaging modalities. We searched PubMed, Embase and Cochrane databases, and processed the results according to PRISMA and GRADE criteria. Ultimately, 31 studies were included that presented original data on the performance of ECG-gated MDCTA, ECG-gated MRA, FDG-PET/CT, and leucocyte scintigraphy in diagnosis of native valve endocarditis, intracardiac prosthetic material-related infection and extracardiac infectious foci in adults. In these studies, we consistently found positive albeit weak evidence for the diagnostic benefit of MDCTA, FDG PET/CT and leukocyte scintigraphy when combined with the modified Duke criteria, alongside expert clinical judgment. Solid data on MRI are scarce. Therefore, we concluded in this chapter that MDCTA, FDG PET/CT and leukocyte scintigraphy should be considered as additional imaging techniques if endocarditis is suspected. Furthermore, we emphasise that these imaging modalities should not be used as a substitute for clinical, microbiological or echocardiographic evaluation, but should instead be integrated in the standard work-up and done together to improve the accuracy of endocarditis diagnosis. MDCTA is an exception, as it can serve as a substitute for TEE in patients in whom this procedure is not feasible. Echocardiography remains the most important tool for detection of endocardial lesions (vegetations, abscesses and perforations) and should be done rapidly and repeatedly if endocarditis is suspected. Concomitant use of imaging techniques providing high-resolution anatomic and metabolic imaging of the heart next to clinical and microbiological data has the potential to increase sensitivity of diagnosis of endocarditis to almost 100%—while simultaneously optimising specificity. This improved accuracy is particularly important in patients with intracardiac prosthetic material because the modified Duke criteria are even less sensitive in this group as compared to patients with native valve endocarditis. However, all imaging modalities come with limitations too. Echocardiography is completely operator-dependent. MDCTA has frequent contraindications. FDG-PET/CT has a compromised specificity due to pathological conditions mimicking a pattern of focally increased uptake and due to difficulty in discriminating aseptic inflammation from infectious process, plus there are currently insufficient clear interpretation criteria for diagnosis of endocarditis. Leukocyte scintigraphy has a limited visibility of smaller infections and vegetations (<1cm), because of its limited anatomical resolution. While

keeping these limitations in mind, we incorporated MDCTA, FDG-PET/CT and leukocyte scintigraphy in our standard workup of patients with a persistent suspicion of endocarditis as we showed them to importantly add diagnostic value in these patients, especially in those with intracardiac prosthetic material *in situ*. We proposed a new and evidence-based diagnostic work-up for endocarditis, including these non-invasive techniques. Our ultimate aim is to better diagnose endocarditis in order to customize therapy (“personalized medicine”).

In **Chapter 3** the first step to reach this aim was described, namely the validation of the newly proposed diagnostic workup for patients suspected of infective endocarditis and/or cardiac device infection. We performed a prospective observational monocenter study to investigate which imaging modalities were performed in the diagnostic workup of 176 consecutively included adult patients suspected of endocarditis/device infection according to the BSAC criteria, after they provided informed consent for inclusion in this study. Most of the included patients (69%) had an imaging workup compatible with the flowchart as it was proposed in chapter 2. Furthermore, 46 of the included patients were eligible for a head-to-head comparison of the stand-alone performance of echocardiography (TTE/TEE), MDCTA, and FDG-PET/CT. Leukocyte scintigraphy had never been performed in the diagnostic workup of patients suspected of endocarditis/device infection, in the time-period of inclusion in the UMCG. Echocardiography (TTE/TEE), MDCTA, and FDG-PET/CT showed sensitivities in patients with native valve endocarditis (NVE) of 71%, 57%, 29% and in patients with intracardiac prosthetic material *in situ* of 75%, 75%, 83%, respectively. The specificity in patients with NVE was 100%, 75%, 100%, and in patients with intracardiac prosthetic material *in situ* the specificity was 86%, 86%, 86%, respectively. In this study we showed that echocardiography was best in assessing vegetations, morphological valve abnormalities and dehiscence, septum defects, fistula formation, pericardial fluid, and ventricular function. MDCTA was best in assessing abscess formation and identified ventricular assist device infection. FDG-PET/CT importantly aided cardiac device infection and identified extracardiac infectious foci as well as alternative diagnosis. Based on the observations in this study, we conclude that the proposed flowchart for diagnostic imaging of endocarditis/device infection is compatible with clinical practice and of added value. Importantly, our data supports that echocardiography, MDCTA, and FDG-PET/CT provide complementary anatomical and functional visualization of endocarditis/device infection and should be performed in each indicated patient with a clinical suspicion, as an addition to clinical and microbiological evaluation.

In **Chapter 4** we focused on one of the imaging modalities investigated in the two previous chapters (2 and 3), namely FDG-PET/CT. In this chapter, we aimed to improve the diagnostic performance of this imaging modality in patients suspected of prosthetic valve endocarditis (PVE), using both visual and standardized quantitative assessments of the scans and the identification of possible confounders. In this multicenter study, patients with a prosthetic valve *in situ* were retrospectively included: 160 of these patients underwent FDG-PET/CT for suspicion of PVE and 77 patients underwent FDG-PET/CT for other indications (the negative control group). The scans of all patients were reassessed, both visually and quantitatively on available EARL-standardized reconstructions (European Association of

Nuclear Medicine Research Ltd.), by two independent observers who were blinded for all clinical data. Confounders were identified using a binomial regression statistical model and scans with identified significant confounders were excluded for the analysis. For the visual assessment of FDG-PET/CT, we found a sensitivity, specificity, positive predictive value and negative predictive value for PVE of 74%, 91%, 89%, and 78%, respectively. Low inflammatory activity (C-reactive protein level of <40mg/L) at the time of imaging and use of surgical adhesives during prosthetic valve implantation were identified as significant confounders. Conversely, recent valve implantation (both within 1 and within 3 months) was disregarded as a significant confounder. After exclusion of the scans with identified significant confounders, diagnostic performance values for the visual assessment increased to 91%, 95%, 95%, and 91%, respectively. Thereby showing that the diagnostic performance of visually analyzed FDG-PET/CT scans for PVE is most reliable in patients with a suspected PVE in which C-reactive protein levels are above 40mg/L and no surgical adhesives were used during the implantation of their prosthetic valve. We additionally showed that the EARL-standardized  $SUV_{ratio}$ , which is a semi-quantitative measure of FDG-uptake, should be equal to or more than 2.0 to predict whether patients suspected of PVE actually have PVE with 100% sensitivity and 91% specificity. Taken together, we conclude in this chapter that both visual and quantitative assessment of FDG-PET/CT have a high diagnostic accuracy in patients suspected of PVE and that it should be implemented early in the diagnostic work-up to prevent negative confounding effects of low inflammatory activity (e.g. resulting from prolonged antibiotic therapy). As opposed to previous reports and thus importantly, did we show that recent valve implantation was not a significant predictor of false positive interpretations of FDG-PET/CT for PVE. Conversely, care should be taken with the interpretation of these scans when surgical adhesives were used during prosthetic valve implantation as these were shown to cause false positive scans.

After the provision of additional support for the use of the non-invasive imaging modality FDG-PET/CT as addition to echocardiography in Chapters 2 to 4, we stated in **Chapter 5** of this thesis that it is now time to truly implement FDG-PET/CT in the diagnostic workup of patients suspected of endocarditis or pacemaker/ICD related infection. We emphasized that this imaging technique should be used in clinical practice, in all suitable patients and as an additional diagnostic tool to both TTE and TEE. The reason for this advice is that FDG-PET/CT provides complementary information about the cardiac as well as the extracardiac infectious state of these patients.

In addition, in **Chapter 6** we explained why physicians should add to their clinical reasoning process the information provided by the functional visualization of intracardiac infection by FDG-PET/CT, to their already obtained information provided by the anatomical visualization by echocardiography. We explained here that evidence for infective endocarditis was historically provided by echocardiography, visualizing structural intracardiac damage, but that technological advances enable visualization of active inflammation caused by cardiac infection with FDG-PET/CT nowadays, even before ensuing structural damage. We should use this knowledge. Even with a lack of evidence for intracardiac structural damage there can be a clear indication for cardiac surgery to prevent further deterioration, as effective treatment with antimicrobial treatment alone can be unsuccessful. In addition, we mentioned in this chapter that

a multidisciplinary Endocarditis Team should be implemented in every large hospital, as recommended by the guidelines from the European Society of Cardiology, 2015. In this multidisciplinary Endocarditis Team, a nuclear medicine physician and a radiologist should be present to explain scan results in weekly team meetings and to inform clinicians about the appropriate indications for their imaging modalities.

In addition to efforts for consolidation of the imaging link to diagnose infective endocarditis, we investigated possibilities to consolidate the microbiological link to diagnose endocarditis in **Chapter 7**. Here, we performed a prospective, diagnostic proof of concept study on explanted heart valves. Two sonication protocols (broth enrichment vs. centrifugation) were compared in 35 negative control valves for contamination rates and in 26 valves from active definite endocarditis patients for added diagnostic value to the standard microbiological workup. We found that the protocol with sonication/enrichment yielded many false positive results in negative control valves (29%; 10/35). False positive results mainly included *Propionibacterium acnes* (currently referred to as *Cutibacterium acnes*) for which we excluded technical problems using next-generation sequencing (no correlation with personnel of the operating room nor with that of the microbiology laboratory). Conversely, the protocol with sonication/centrifugation yielded acceptable false positive rates (11%; 4/35) and was regarded as the best protocol for sonication of heart valves with infective endocarditis. Compared to direct culture solely, adding sonication/centrifugation (a protocol that also includes molecular testing) significantly increased the diagnostic yield from 6/26 to 17/26 valves ( $p=0.003$ ). Most importantly, culture positives almost doubled (from 6 to 10), providing unique quantitative information about antimicrobial susceptibility. And even if direct molecular testing on the heart valve was added to the standard workup, sonication/centrifugation provided additional diagnostic information in a significant number of valves (8/26; 31%;  $p=0.013$ ). Therefore, we concluded in this chapter that sonication/centrifugation added relevant diagnostic information in the workup of heart valves with infective endocarditis, with limited contamination rates.

### Therapeutic possibilities in infective endocarditis

The second part of this thesis focused on improved therapeutic possibilities in endocarditis, both medically and surgically.

In **Chapter 8** we performed a retrospective observational two-cohort study that aimed to increase the therapeutic efficacy of gentamicin in endocarditis by the optimization of its dosing regimen. The first cohort was used to parameterize by iterative two-stage Bayesian analysis an endocarditis population pharmacokinetic model of gentamicin in treatment of endocarditis. The second cohort was used to validate and compare this new endocarditis population model with the two already existing population models for patients admitted on an intensive care unit or a general ward, respectively, for their accuracy to predict serum gentamicin levels. The statistical criteria “Akaike Information Criterion” and “the weighted sum of squares of the residuals divided by the degrees of freedom” were used to select the endocarditis model with the best prediction of serum gentamicin levels in the 65 included patients in our first (modeling) cohort. The endocarditis model that we built had a fixed value of 0.277 L/h/70kg for

metabolic clearance, and Bayesian fitting with a value of 0.698 ( $\pm 0.358$ ) for renal clearance as fraction of creatinine clearance, and a value for volume of distribution of 0.312 ( $\pm 0.076$ ) L/kg corrected lean body mass. After modeling the endocarditis model, we externally validated all three population models (for patients with endocarditis, for patients admitted on an intensive care unit, and for patients admitted to a general ward) with data from the 14 patients included in the second (validation) cohort. Using the statistical criteria of "Median Prediction Error (MDPE)" and "Median Absolute Prediction Error (MDAPE)", we showed a similar predictive power of the endocarditis model (MDPE -1.77%, MDAPE 4.68%) as compared to the intensive care unit (MDPE -1.33%, MDAPE 4.37%) and general ward (MDPE -0.90%, MDAPE 4.82%) models. All three models acceptably predicted pharmacokinetic parameters for gentamicin in endocarditis patients. Nonetheless, we noticed that the endocarditis patients appeared to have an increased volume of distribution, similar to that of intensive care patients. Volume of distribution mainly determines the height of the peak of the gentamicin serum levels, which in turn correlate with bactericidal activity. Therefore, as the aim is to achieve sufficient bactericidal activity to treat endocarditis properly and in order to maintain simplicity, we advised to use the already existing intensive care unit model for use in clinical practice to avoid underdosing of gentamicin in endocarditis patients.

In **Chapter 9** we described a series of sixteen surgically treated endocarditis patients with the use of intra-operative and high quality macroscopic pictures. All these patients had active native or prosthetic aortic valve endocarditis complicated by perivalvular abscess formation at various locations and to different extents and extensive destruction of the left ventricular outflow tract. In addition, all of these patients underwent surgical treatment of their endocarditis and a stentless bioprostheses as aortic root replacement was implanted. 14 males and 2 females were included from 2006 to 2015, with a median age of 63 years old [range 31-77]. Affected valves comprised 4 native and 12 prosthetic aortic valves, and predicted operative mortality was high with a median logarithmic EuroSCORE I of 41 [range 13-68]. Patients presented with a wide variety of surgical indications. Anatomical destructions included aortoventricular and aortomitral dehiscence, septum derangements, Gerbode defect (a shunt from the left ventricle to the right side of the heart) with accompanying total atrioventricular conduction block, and mitral and tricuspid valve involvement. In this series, the in-hospital mortality rate of 18.8% and the 30-day mortality rate of 12.5% were relatively low. Therefore, we concluded that active aortic valve endocarditis complicated by paravalvular abscess formation and destruction of the left ventricular outflow tract remains to be a therapeutic challenge for which repair with stentless bioprostheses is a valuable option, both for affected native and prosthetic valves. The use of the stentless bioprosthesis allows for a radical and relatively standardized surgical approach with high success rate for complete debridement, is readily available and yields comparable clinical outcomes to the historical gold standard, repair by homografts. Of note, and in addition, use of one type of prosthesis reduces logistical issues and purchasing costs.

### **Future perspectives for the improvement of care for infective endocarditis**

We developed clearly defined concepts on how to improve important links in the chain of care (clinical

pathways) for patients with (suspected) endocarditis. In the third part of this thesis, some ideas for future improvement are discussed.

In **Chapter 10** we elaborated on the most recent update of the guidelines for the management of patients with endocarditis, in which an Endocarditis Team is put forward as a part in the improvement of care for patients with (suspected) endocarditis. These guidelines again emphasize that endocarditis requires a multidisciplinary approach since patients present with highly variable signs and symptoms, need a high-standard of care from several medical specialists, and need to be discussed in a surgical team early in the course of the disease. Observational studies support the implementation of a multidisciplinary Endocarditis Team by showing a marked decrease in mortality rate after discussing endocarditis patients in such a setting. Based on our experience with the implementation of this team in the regions Rotterdam-Rijnmond and Groningen, the Netherlands, we formulated some important pillars and advice for difficulties that might potentially be encountered. As important aspects for the structure and function of an Endocarditis Team we elaborated on the tasks and construction of an Endocarditis Team, the characteristics of a reference center, the selection of patients, and the meetings of an Endocarditis Team. Furthermore, as the setting up of an Endocarditis Team can be difficult, we gave some advice about its start, finding the optimal moment for meetings, how to manage the infrastructure of patient application and which clinical data is minimally required, how to approach acute patients, coordination and organisation of team meetings, and feedback from the team's discussion to the treating physicians. The writing of this manuscript helped us to set up and optimize the Endocarditis Team in our own centers, we hoped to support the physicians in other hospitals trying to set up their own team, and ultimately we aimed to improve the provided care for patients with (suspected) endocarditis in the Netherlands.

In **Chapter 11** we stated that currently available imaging modalities, both anatomical and functional, are insufficiently capable of distinguishing sites of bacterial infection from sterile inflammation. Therefore, at present, definitive diagnosis of any infection can often only be obtained by tissue biopsy and subsequent culture and, occasionally, a definite diagnosis even appears to be impossible. Therefore, we stated in this chapter that novel imaging modalities are needed to accurately diagnose bacterial infections early. In this regard, we mentioned bacteria-targeted imaging as an attractive option due to its specificity. As a more specific diagnosis could prove critical in a current and vast amount of remaining cases with diagnostic uncertainty, targeted imaging represents an appealing option for diagnosis. For example, targeted imaging could disclose the pathogenic bacterium in patients with negative blood cultures so that adequate antibiotic therapy can be given. Also, targeted imaging could point towards additional and distant sites of infection more specifically than FDG-PET/CT and these infectious sites should be taken into account in the individualized therapy plan. On top of these benefits intra-operative targeted imaging might be able to visualize the exact borders of infected tissue of which radical resection could potentially improve patient outcome. The application of intra-operative targeted imaging is likely to be highly important in endocarditis also, since it is mandatory during cardiothoracic surgery to immediately implant prosthetic material in the infected area as replacement of removed tissue and



to restore vital cardiac function. However, from the reviewed data in this chapter it became clear to us that it is still difficult to predict which tracers or modalities will prove most appropriate for clinical use in the future. Nevertheless, further investigation and implementation of new imaging techniques, such as multi-modality or optoacoustic imaging and smart activatable tracers, holds great promise for quick and accurate detection of infections. In addition, implementation of new imaging techniques may ultimately be extended to antibacterial therapy, for example in the form of targeted photodynamic therapy.

## Discussion

### Effects on daily clinical practice of the work covered in this thesis

To a large extent results of this thesis have been implemented into clinical practice at our center.

#### *Endocarditis protocol UMCG*

In our center in the Netherlands, the UMCG, we implemented a clinically focused protocol aiming to guide all physicians in our hospital who deal with patients with (suspected) infective endocarditis. This protocol is regularly updated to cover the optimal diagnostic and therapeutic workup. The protocol explains the signs and symptoms of endocarditis, includes criteria for consideration and investigation of possible infective endocarditis, advises about which diagnostic tests to use, which medical specialists to consult, which therapeutic drugs to start, and when to perform cardiothoracic surgery. Furthermore, it provides criteria about the follow-up of patients during hospital admission and after discharge. We updated this clinical “Endocarditis protocol UMCG” twice in the last four years, largely based on the study results depicted in this thesis. First, our advice for the indications of using non-invasive imaging modalities in addition to echocardiography in the diagnostic workup of patients suspected of endocarditis, as presented in the diagnostic flowchart in Chapter 2 of this thesis, was incorporated. Second, the starting dose for antimicrobial treatment with gentamicin is now advised as 4 mg/kg body weight (as opposed to 3 mg/kg previously) based on our population pharmacokinetic modeling study present in Chapter 8 of this thesis.

#### *Harmonization of the one-stop-shop protocol for concurrent FDG-PET/CT and MDCTA scanning*

In the UMCG we developed and implemented a joint scan protocol for diagnostic MDCTA imaging of the heart and FDG-PET/CT imaging of the whole body for patients with (suspected) endocarditis in which imaging with both of these modalities is indicated by the diagnostic flowchart. The implemented scan protocol facilitates adequate imaging by means of a “one-stop shopping” principle. The combined use of FDG-PET/CT and MDCTA provides high-resolution metabolic and anatomic information and due to the development of newer and hybrid camera systems, it is possible to perform both modalities in a single visit. Advantages of this simultaneous acquisition are improvement of patient comfort, easy overlay of both scans due to an identical patient position and thereby fast synergistic diagnostic results. Essential for an assessment of these scans with good accuracy for endocarditis, is a proper preparation of the patient.

### *Endocarditis Team UMCG*

As extensively discussed in Chapter 10, the current European and American guidelines recommend setting up an Endocarditis Team in reference centers. These centers should have direct access to diagnostic procedures such as TTE, TEE, MDCTA, MRI, FDG-PET/CT, and leukocyte scintigraphy, should have direct access to cardiac surgery, and several specialists should be present on site, including cardiac surgeons, cardiologists, infectious disease specialists, microbiologists, specialists in echocardiography and other cardiac imaging techniques. Since we have been conducting scientific research in our IDENTICAL research team for four years already, we were enthusiastic to extent this cooperation also to the clinical setting for the medical care of patients with (suspected) endocarditis. At the UMCG we already had the infrastructure of a well-functioning Endocarditis Protocol and a well-functioning Infectious Diseases meeting once a week in which (suspected) endocarditis patients are also discussed. Nevertheless we experienced several obstacles in the setting up of a well-functioning Endocarditis Team in the UMCG, such as finding a time-point for a meeting which fits the work-schedules of all medical disciplines involved, finding a proper coordinator for the team and the financial reimbursement for his/her efforts, and development of a fitting infrastructure for the application of new patients which is compatible with good clinical practice (especially for acute patients) and at the same time practically achievable (compatible with other tasks of the person for application and the capacity of the hospital for admission of patients). This struggling has probably been due to the fact that only a limited number of people are involved in the IDENTICAL research team, and these people alone are not able to be present at all meetings all the time. Therefore, the development had to be taken at a higher level and each department had to feel the need for an Endocarditis Team and provide man power accordingly. First, somebody had to be responsible for the arrangement of the regular meeting of the Endocarditis Team and this person needed to get the time for this important function. Second, on the departmental level people had to be persuaded about the importance of a well-functioning multidisciplinary cooperating Endocarditis Team on the regional level. Fortunately, we can safely state now that we have been able to formally install an active, dedicated Endocarditis Team in the UMCG, with a separate time slot to discuss signed up patients with (suspected) endocarditis from our own center and from the region.

### **Future perspectives**

#### *Completion of diagnostic research*

Some investigations that we already started need completion. One of these projects is the investigation of the exact role of TEE in patients with *Staphylococcus aureus* bacteremia in our center. *Staphylococcus aureus* bacteremia (SAB) is a very serious infection that is closely related to infective endocarditis, as SAB causes endocarditis in 15% of cases. To guide physicians in our hospital who take care of patients with SAB, a clinical SAB protocol was set up in the UMCG. As a comparatively high percentage of SAB patients present with or develop endocarditis, some experts argue, based on a large body of evidence, that every patient should be thoroughly examined, including TEE. On the contrary, others state and studies support the notion that TEE could be disregarded in well-selected patients with SAB who have a low risk of developing/presenting endocarditis. To further investigate this issue, the value of TEE in SAB is investigated in our population of patients using the electronic IDENTICAL-database.

A second on-going project is the investigation of the optimal time to perform FDG-PET/CT scanning in patients with suspected infective endocarditis. Currently, standard imaging is performed 1 hour after FDG-injection. However, several studies (for other indications) suggest an increase in diagnostic accuracy when imaging at a later time point.<sup>1,2</sup> In the EANM/SNMMI guideline for the use of FDG in inflammation and infection,<sup>3</sup> use of dual-time point scanning is mentioned but not as standard practice. Theoretically, delayed scanning could increase the diagnostic accuracy by maximizing the target-to-background contrast, due to continued clearance of background activity in the blood pool.<sup>1,2,4,5</sup> Indeed, it may be inferred that FDG-uptake by activated monocytes/macrophages continues to increase even at 3 hours post injection.<sup>2</sup> In addition, we hypothesize that more time is needed for macrophages to take up FDG after administration of antimicrobial agents. Therefore, we aim to investigate the accuracy of the standard acquisition at 1 hour after FDG-infusion and of a second acquisition at 3 hours after FDG-infusion in patients from the UMCG. In light of the difficult diagnosis of endocarditis, we reasoned that even small differences between two scans from consecutive acquisition times might provide important information. This study is still in progress and needs completion. Thereafter, a next step would be to clarify the optimal acquisition time (e.g. in between 1 and 3 hours after FDG-injection). As delayed scanning requires a longer acquisition, the right balance between optimal sensitivity and optimal acquisition needs to be clarified in larger series by dynamic or sequential FDG-PET/CT scanning.<sup>2</sup>

#### *Suggestions for diagnostic research*

In addition to the two above-mentioned projects, there are many other areas of investigation interesting to pursue. On the diagnostic part, we could first of all extend the research described in chapters 1 and 2 of this thesis and provide a modified version of the proposed flowchart with an indication of the patient flow by thickness/color of the arrows/fields in order to show real life data. In this modified flowchart, fields and arrows pointing towards leukocyte scintigraphy would fade for example, based on the data presented in chapter 3 of this thesis. In addition, there is a call for clarification about the optimal window of time to perform imaging, both for the initial echocardiography, MDCTA, FDG-PET/CT and leukocyte scintigraphy as well as their repetition if this is indicated. These data would be an important addition to the proposed flowchart in chapter 2 in this thesis as well. Also, there is a need for the optimization and standardization of patient preparation for FDG-PET/CT scanning. Furthermore, elucidation is wanted about the best MDCTA and FDG-PET/CT acquisition and reconstruction protocols for imaging of endocarditis as well as their interpretation, to even better identify false positive and false negative results. Investigation into the standardization of visual pattern recognition to diagnose endocarditis should be pursued and potential sources of false FDG-PET/CT results should be better established. Especially interesting in this regard is the effect of antimicrobial therapy on the sensitivity of FDG-PET scanning, also in view of using this modality in monitoring disease activity and response to treatment. Furthermore, more information is needed on the benefits and drawbacks for the use of FDG-PET/CT to identify systemic infectious foci. Finally, we need to elucidate when FDG-PET/CT and MDCTA lead to important changes in the therapeutic plan for patients. All of these questions would almost certainly differ between subgroups of patients (e.g. those without vs. with intracardiac prosthetic material) and therefore focused research in these different groups of patients would be helpful.

There are also other imaging techniques available to investigate for the diagnosis of endocarditis. As already shortly mentioned in the introduction, there is 3D echocardiography providing high-quality real-time TEE. The first studies about MRI in endocarditis show a delayed contrast enhancement of the endothelial lining depicting antegrade and retrograde dissemination, paravalvular tissue extension, subendocardial and vascular endothelial involvement in endocarditis.<sup>6</sup> Furthermore, MRI potentially enables dynamic measurements and magnetic resonance spectroscopy (personal communication, Dr. Ronald J.H. Borra, UMCG, the Netherlands). Other opportunities to investigate for diagnostic use in endocarditis include true hybrid-PET/MRI and labeled leukocytes combined with PET-scanning. Finally, phase-contrast CT might become feasible for diagnostic use in endocarditis with the newer generation machines that enable increased scanning speed, higher resolution and improved detectors, thereby substantially reducing the required radiation dose (personal communication, Prof. Rajiv Gupta, Massachusetts Gen Hospital and Harvard Medical School, Boston, USA). Finally, visualization of infected tissue by tracers, such as <sup>18</sup>F-labeled vancomycin, might be a targeted opportunity to accurately diagnose endocarditis.

Non-imaging opportunities for improvement of the diagnostic accuracy in endocarditis include further optimization of sonication protocols. In addition, we should establish more solid criteria to discriminate between contamination versus identification of pathogens causing infection in future research. Further investigation about the origin of *Propionibacterium acnes* (currently referred to as *Cutibacterium acnes*) and its relevance in diagnostic samples would be especially pressing within this investigation. Possibly less catchy, but very important, would be the investigation on how to improve diagnostic testing. Especially pressing are opportunities to achieve blood culture diagnostics of sufficient quality, for which we could possibly collaborate with behavioral sciences. Use of more culture-independent tests, for example using molecular testing, in addition to cultures is an opportunity to increase diagnostic yield and should therefore be pursued. Finally, another interesting field to further explore involves the use of biomarkers to diagnose endocarditis, and identifying pathogen response as an early surrogate parameter for microbiological response.

Combining imaging and non-imaging opportunities for improvement of the diagnostic accuracy in endocarditis, sonication with the concomitant use of probes, e.g. for nuclease, could be an interesting mode of targeted imaging that is worth to pursue. This technique could quickly identify selected bacteria before any microbiological processing (e.g. culture). Ideally, a combination of methods would be available for monitoring of treatment success. This would potentially allow to tailor duration of therapy to individual patients and to objectively identify patients who would require suppression therapy. This last group of patients consists mainly of patients with prosthetic material *in situ* without surgical source control.

#### *Suggestions for therapeutic research*

Several research questions are important for future research concerning the correct treatment in this patient group. One interesting research question is the outcome of the patient after second or third

lines of treatment for intracardiac prosthetic material related infection, as compared with the first line of treatment. As a general rule, first line treatment for intracardiac prosthetic material related infection consists of surgical prosthesis removal combined with appropriate antimicrobial therapy. The exception is uncomplicated prosthetic valve endocarditis as it has a fair chance of successful medical treatment alone (>50%, depending on the micro-organism involved). However, although there is evidence and consensus with regard to the first line of treatment, surgical removal is not always possible because of its associated high risk, technical limitations, and lack of willingness to undergo an invasive surgical procedure. Therefore, second and third lines of treatments exist that do not include surgery but consist of antimicrobial therapy with biofilm-penetrating agents during a predetermined timespan (second line) or a life-long suppressive therapy (third line) alone. These treatments are considered suboptimal and have not been extensively investigated to date. Therefore, optimization of alternative treatments and their indications need to be investigated.

One step in the optimization of the antimicrobial treatment for endocarditis patients, in particular those with intracardiac prosthetic material, includes the use of therapeutic drug monitoring. Fixed drug dosage may result in different, and probably suboptimal, systemic and tissue concentrations of antimicrobial agents,<sup>7</sup> as both pharmacodynamic and pharmacokinetic parameters differ within and between individuals.<sup>8</sup> In critically ill patients for example, changes in their volume of distribution and clearance of antimicrobials affect the antimicrobial concentration at the target site, resulting in antimicrobial underdosing and consequent therapeutic failure and/or the development of antimicrobial resistance.<sup>8</sup> Conversely, therapeutic drug monitoring (TDM) consists of individualizing drug dosages with the aim of maximizing the efficacy of treatment and minimizing toxicity by measurement of achieved target plasma concentrations.<sup>7,8</sup> TDM asks for target plasma concentrations for the antimicrobial agents used, and therefore we propose to investigate for which peak blood concentrations of gentamicin we should aim in endocarditis and whether the cumulative area under the curve for gentamicin serum concentration correlates with patient survival. Also, we propose to investigate how to optimize dosing and dosing regimens of other commonly used antimicrobial agents based on PK/PD evidence. In this regard, commonly used groups of antibiotics include beta-lactams (e.g. flucloxacillin, amoxicillin, penicillin and ceftriaxone), glycopeptides (e.g. vancomycin) and others (e.g. rifampicin). Furthermore, we would propose to conduct this research stratified for patient groups, e.g. for NVE vs. PVE. Notwithstanding the importance of this research, the ultimate aim is to reach therapeutic antimicrobial concentrations not in the blood (the derivative medium) but in the endocardial tissue that is infected. Therefore, we propose to investigate what concentration of different antimicrobial agents is achieved in infected cardiac tissue of endocarditis patients who have received antimicrobial therapy for a certain time already. Resected endocardial material from these patients (e.g. heart valve, vegetation, biofilm formed on prosthetic material obtained during surgery on medical indication) can be studied *in vitro* for antimicrobial and viable microbial concentrations.

Other suggestions for research about the antimicrobial therapy of endocarditis include elucidation of criteria to safely treat patients with a shorter course, for example stratification based on risk or

response scores. Other research aiming at improvement of antimicrobial therapy includes exploration of possibilities for pre-treatment or co-treatment with biofilm-disrupting agents. Conversely, a suggestion to improve the surgical therapy of endocarditis encompasses optimization of the indication and timing for surgery, taking into account mortality rates of performing versus withholding cardiothoracic surgery for specific patients. Finally, as for the diagnosis of endocarditis, biomarkers are an interesting field to explore for use in the monitoring of therapy.

#### *Suggestions for prophylaxis research*

During this PhD-project we have not addressed endocarditis prophylaxis. However, in light of the contradicting reports that have been published recently about the ability to prevent endocarditis with the prophylactic administration of antibiotic agents before procedures known to cause bacteremias, more studies to clarify this issue would be of help. In this regard, we should get to know whether we could best invest in prophylaxis of endocarditis or conversely optimize our ability to diagnose and treat endocarditis early, as proposed by the NICE consortium.

There are additional interesting fields to explore, aiming at prevention of endocarditis development. In light of the increasing number of prosthetic material implanted within the heart of the aging population of the Western world, it is tempting and lucrative to investigate tissue engineering, specific coatings and materials that are able to decrease the incidence patients with intracardiac prosthetic material in which endocarditis develops. This area could be explored in collaboration with the medical specialties of orthopedic, trauma and vascular surgery since there are many commonalities between these fields, most importantly with regard to the implantation of foreign materials within the human body.

## Conclusion

In conclusion, this thesis emphasizes that infective endocarditis is a disease that can be life-threatening and deserves an aggressive diagnostic and therapeutic workup in clinical practice. Unfortunately, current clinical practice is not yet fully optimized and there is a clear need for improvement of the medical care for patients with (suspected) endocarditis. Therefore, we set up a multidisciplinary study group of representatives from clinically cooperating medical departments for research on infective endocarditis, the IDENTICAL study group.

In this thesis we showed improvement of the diagnostic workup of (suspected) endocarditis patients by using non-invasive imaging techniques (FDG-PET, MDCTA and leukocyte scintigraphy) in addition to echocardiography (**Chapters 2-5**), which also leads to changes in the individual treatment of patients accordingly (**Chapter 6**). Furthermore, application of sonication of surgically explanted heart valves lead to improvement of the microbiological identification of pathogens (**Chapter 7**). We showed that optimization of antimicrobial therapy with dosing gentamicin according to the intensive care unit population pharmacokinetic model (e.g. prescribing 4 mg/kg as a starting dose) led to an improvement

of the obtained serum levels in endocarditis patients (**Chapter 8**). Furthermore, repair of active aortic valve endocarditis complicated by paravalvular abscess formation and destruction of the left ventricular outflow tract with stentless bioprostheses was shown to be a valuable option for a more standardized approach to the surgical correction of both native and prosthetic valves (**Chapter 9**).

The proposed changes for optimization of (suspected) endocarditis patients care encompass changes of paradigms in clinical practice and therefore need some convincement and encouragement (**Chapters 5, 6, 9**). Ultimately, regular multidisciplinary Endocarditis Team meetings are needed to share information among experienced specialists and to reach a final diagnosis and therapy for each individual patient (**Chapter 10**). In addition, future scientific investigation should focus on further optimizing clinical care and strengthen the chain links of the in-hospital process of events for patients with (suspected) endocarditis (**Chapter 11-12**). Clinically and practically important changes in daily care of patients with infective endocarditis were already accomplished by the research performed in this thesis leading to updates of our hospital protocol for endocarditis (**Chapter 12**).

Altogether, we think that the research presented in this thesis is important to create opportunities for improvement of care for patients with (suspected) endocarditis. Ultimately, our efforts should lead to an ideal world in which the chain of care for patients with endocarditis is well organized and each link is optimized. Most importantly, the involved medical specialties collaborate in a multidisciplinary team in which communication is open, fair and aimed at providing the best care for each individual patient with (suspected) endocarditis. Each physician should have a low threshold of including infective endocarditis within his/her differential diagnosis. If a patient is suspected of endocarditis, the diagnostic workup should be started rapid to obtain a better picture about the disease of and best care for the patient. Diagnosing endocarditis involves calculating odds, therefore asking for a complete diagnostic workup with an optimal performance of each individual test and a multidisciplinary discussion for the correct interpretation and weighing of results. A complete diagnostic workup includes extensive imaging and sonication of an explanted heart valve, if available. If a patient gets diagnosed with endocarditis, the regimen for antimicrobial therapy should be formalized according to the best fitting population pharmacokinetic model, if available. The need for cardiothoracic surgery should be discussed in the Endocarditis Team early in the course of disease.

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